AMENDMENTS TO THE DRAWINGS

Please replace original drawing sheets 1-9, corresponding to original Figures 1-9, with the attached replacement sheets 1-9. The headers of the attached replacement sheets have each been labeled "Replacement Sheet."

REMARKS

Claims 1, 3, 4, 6, 7, 9, 27 and 28 previously were presented. Claims 1, 6, 7 and 27 have now been amended. New claims 29-33 have been added. All independent claims and accordingly all presented claims now are limited to dosage forms for intranasal, transdermal, or intradermal administration. In order to promote prosecution, and reserving the right to reintroduce the coverage in a continuation application, all prior claim language broad enough to embrace buccal administration (through the mucosa of the mouth) as allegedly taught by the applied Stanley reference, now has been deleted. The dose forms as now claimed must be intranasal, trans-dermal, or intradermal dosage forms.

The proviso language from claim 1 that was objected to by the Examiner also has been deleted. The inventor and his undersigned representative, apparently erroneously, understood this language to have been suggested by Examiner Tate. In its place applicant proposes to amend all claims to cover dosage forms which establish a steady blood concentration from the lower ranges recited to *a maximum* of about 10 pg/ml. Applicant submits this is supported by an objective reading of the specification as filed, and overcomes the new matter rejection.

New claims 29-33 have been added and claims 6 and 7 amended to cover dose forms regarded by Applicant as currently particularly preferred. For basis, see the specification as filed at page 24 (administration modalities), 25 (amounts of active), and 36 (preferred duration).

Applicant has also replaced the drawings as originally filed with replacement sheets. The replacement sheets have been reformatted to facilitate the visual identification of lines present in the original drawings.

The amendments to the claims and the replacement drawings introduce no new matter into the application.

Objection to the drawings

The Office action objected to the drawings, alleging that the identification of particular lines in the figures was difficult. Applicant has attached reformatted replacement sheets of drawings to this amendment.

In view of the replacement sheets, Applicant respectfully requests that the objection to the drawings be reconsidered and withdrawn.

Status of the claims

In summary, the various claims as previously presented stand rejected under sections of the statute set forth below.

1. Claims 1, 3, 4, 6, 7, 9, 27 and 28 stand rejected for new matter or lack of written description under 35 USC 112, first paragraph;
2. Claims 1, 3, 4, 6, 7, 9, 27 and 28 stand rejected for lack of enablement under 35 USC 112, first paragraph;
3. Claims 1, 3, 4, 6, 7, 9, 27 and 28 stand rejected for indefiniteness under 35 USC 112, second paragraph;
4. Claims 1, 6, 7, 9, 27 and 28 stand rejected as anticipated by Stanley (4,863,737); and
5. Claims 1, 3, 4, 9, 27 and 28 stand rejected as anticipated by Dixon.

In addition, the Examiner cites but does not apply the Cort Patent number 4,263,283, (a nose drop formulation), the MedSafe Minirin Nasal Spray document from Ferring Pharma (describing a commercially available nasal spray), Flockhart (5,298,256, disclosing a buccal patch), and Harris (5,482,931, Example 1-nasal spray compositions).

Reconsideration and withdrawal of all rejections is respectfully requested in view of the amendments offered above and the following arguments.

Claims 1, 3, 4, 6, 7, 9, 27 and 28 stand rejected for new matter and failing to comply with the written description requirement

The alleged new matter (the proviso language) has been deleted from claim 1, thereby obviating this rejection as to claim 1 and its remaining dependent claims 3, 4, 6, 7, and 9. The undersigned assumes that the inclusion of claims 27 and 28 in the new matter rejection was an inadvertent mistake, as the alleged new matter identified by the Examiner did not appear in those claims, and all the limitations of these claims have clear basis in the specification as filed.

The remaining lack of written description objection/rejection, to the extent applied to the claims as amended, is respectfully traversed. Every limitation of every presented claim is clearly and unambiguously recited as an alternative aspect of Applicant's invention in the specification as filed. The claims define the invention, and the specification clearly and unequivocally recites the subject matter now claimed. As the Examiner states, Applicant must describe his invention "with all its claimed limitations" and this he has done. Applicant's invention is not a chemical genus - only one well known and commercially available chemical is recited, desmopressin, and no organic formula is required to describe it. The limitations and description of his invention clearly are sufficient to distinguish his invention, i.e., that which is claimed, from the prior art. The genus claimed herein is the set of dosage forms meeting the structural and functional limitations specifically recited in the application as filed and in the claims as now presented. Applicant submits there is no valid precedent for application of a lack of written description rejection to the claims as amended, and that to do so would abrogate a century of law relating to constructive reduction to practice. Applicant requests reconsideration and withdrawal of this rejection to the extent applied to the claims as amended.

Applicant suspects the basis and motivation for this rejection lies in the Examiner's statement that "the art clearly teaches compositions comprising desmopressin at the required concentrations in the composition, and thus under inherency, it must function as claimed." Applicant agrees that the art teaches desmopressin compositions containing amounts of desmopressin which overlap with the amounts recited in some of the presented claims. However, the Examiner's next statement that "under inherency, it must function as claimed" is incorrect, because it does not take into account bioavailability in terms of controlling the onset and offset of the pharmacodynamic antidiuretic activity. This issue is discussed in more detail below.

Claims 1, 3, 4, 6, 7, 9, 27 and 28 stand rejected for lack of enablement

Applicant submits that his specification, taken together with the knowledge of those skilled in the dose formulation art, is sufficient to enable persons of skill in the art to make and use the full scope of the subject matter claimed. It is well established law that whether an

application meets the enablement requirement of 35 USC 112 requires assessment not only of the scope and content of the specification but also of the background knowledge of the art. Applicants are not required to teach specifically how to make or use components of a claimed invention that are already known to persons of skill. "[A] patent need not teach, and preferably omits, what is well known in the art, *Hybritech v Monoclonal Antibodies, Inc.*, 802 F.2nd 1367 (CAFC, 1986).

Applicant does not regard his invention as comprising the particular structure his claimed dosage forms take, beyond the recited specific language of the claims limiting the dose to various suitable forms for intranasal, transdermal, or intradermal use as, and the requirement that the dose forms establish in a patient who uses them a plasma/serum desmopressin concentration within the ranges recited, optionally for the times recited. Applicant submits there is a wealth of transdermal and intradermal patch devices and other transdermal and intradermal drug administration devices disclosed in the patent and other literature. There also are many patents in the prior art disclosing nasal administration technologies including nasal spray apparatus and formulations. Multiple US and foreign companies sell dose form technology, and there are many known specific ways to produce desmopressin dosage forms having the properties required by the claims. The purpose of these technologies, broadly speaking, is to provide various means to enable a patient, typically under the care of a physician, to achieve a desired concentration or concentration range of a desired drug in his or her circulation. Any given dosage form of any given drug necessarily will be characterized by an inherent bioavailability, dictated by the structural and chemical properties of the dose forms, by the route of administration, and by the properties of the particular drug being administered. Because blood volume differs in different patients (in a child, versus a juvenile female, verses a large mature male, for example), it is well known that different specific dose forms are required to attain a given therapeutic plasma/serum concentration in these respective patients.

Applicant's insight is that far smaller doses of desmopressin than are normally administered clinically, i.e., doses which achieve a plasma/serum concentration in the ranges recited in the claims and which maintain that blood concentration for some predictable, consistent, and reasonable time, have unexpected properties. Such low doses are not only sufficient to induce antidiuresis, but also to reduce or eliminate the risk that a patient may

experience hyponatremia. Stated differently, they uncouple the antidiuretic effect of desmopressin from its hyponatremia-inducing effects.

Note also that, for example, intranasal, intradermal, and transdermal dosage forms normally will comprise different amounts of active if they are to produce the same blood concentration in a given patient, because normally the bioavailability of a given drug will be different for each form. A form characterized by low bioavailability must contain more active than a form with higher bioavailability to achieve a given blood concentration. Stated differently, one can achieve the same blood concentration in a patient using any of the dosage forms set forth in the claims by varying the amount of active appropriately.

Thus it can be appreciated that the precise structure of a dose form embodying applicant's invention can vary significantly. The particular mechanism or structure through which the dose forms as claimed achieve the required blood concentrations do not and need not limit the invention. Rather the invention lies in dose forms that achieve and maintain for a reasonable time, by any known means or means yet to be invented, concentrations within the claimed range.

This novel effect can be achieved, for example, by administering an intranasal, transdermal, or intradermal dose form that delivers a *bolus* of the drug to obtain a concentration within the range, e.g., at the mid or higher end of the range. The patient then will experience an antidiuretic effect during a time interval – starting when the concentration of the drug in his or her blood exceeds the concentration necessary to activate kidney water channels, and continues while the blood concentration reaches a maximum as drug builds up in the bloodstream. The maximum must not be significantly above 10 pg/ml, i.e., high enough to approach the blood concentrations achieved in prior art doses of desmopressin. The antidiuretic effect continues as the concentration falls from the maximum achieved by the bolus as the drug is cleared naturally from the body, and ends when the concentration of active falls below the water channel activation level. When this occurs, normal urine production is restored. Thus, the chances that the patient will develop hyponatremia are diminished because he or she "automatically" returns to homeostasis in a relatively short time, because blood concentration is never so high as to endure above the threshold for an undesired long time interval.

Alternatively, the effect can be achieved by *sustained* intranasal, transdermal, or intradermal administration at a low level just sufficient to maintain the plasma/serum concentration some reasonable amount above the threshold. In this instance, while the administration is in progress, antidiuresis is established. When the administration interval terminates, normal urine production returns quickly as the desmopressin blood concentration is already low, and need not fall very far through normal clearance mechanisms to permit renewed urine production.

Dosage forms which achieve the novel effect discovered by Applicant can be made simply by lowering the amount of active in a selected known dosage form, taking into account the characteristic bioavailability of small peptides in that particular dosage form. Applicant submits that much of the dosage form technology developed for administration of polypeptides over the last 20 years is directed to improving their bioavailability, i.e., to devising technology which will assure that a greater amount and more uniform amount of active in the dose form will actually reach the blood stream where it does its work. Advantageously, with Applicant's invention, it is important that *less desmopressin* actually reaches the blood stream than is normally administered. This means that the manufacture of dosage forms, if anything, is *easier* than similar dosage forms designed for administration of polypeptide drugs that must be present at higher blood levels.

The skilled drug formulator is aware of many options available to make various embodiments of the subject matter claimed without the exercise of invention. No undue experimentation is required. All that is required is the well known normal path of development and empirical refinement normally done in the development of any drug dosage form. In support of this point, applicant has submitted the declaration of Dr. Nardi, a person of skill in the art, who declared:

> As a person of skill in this art, I can state without reservation that skilled persons were able, at the time the application was filed, to make various dosage forms adapted for intranasal, transmucosal, transdermal, conjunctival, or intradermal administration that will maintain in a patient a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per ml plasma/serum to about 10.0 picograms desmopressin per ml plasma/serum. Given the clearance rate of desmopressin (on the order of a 1.5 to 2.5 hour half-life in humans), this could be done simply by reducing the amount and/or concentration of active in a selected dosage form appropriately. Over the

> last 30 years the industry has developed sophisticated transmucosal drug delivery technology including intranasal, buccal, and sublingual dosage forms (as described in the specification of this application), as well as intradermal and transdermal dosage forms. These provide a large number of options for the preparation of low dose desmopressin dosage forms having the properties set forth in the claims.

As further evidence of Applicants contention and belief that persons of skill can manufacture and use numerous dosage forms falling within the claims, and by way of non limiting example, the Examiner is invited to review US 7,244,703 (Bentley). It discloses intranasal dose technology, and states (emphasis supplied):

> More particularly the invention relates to compositions and methods for the delivery of *peptide drugs*, peptidomimetics, or proteins through the nasal mucosa. The pharmaceutical compositions of the present invention include a permeation enhancer, that is, a material which is capable of increasing the rate of passage of the peptide through the nasal mucosa.
>
> In accordance with the invention, there is provided a pharmaceutical composition for treating a patient comprising: (A) *a pharmaceutically active peptide*; (B) a permeation enhancer; and (C) a liquid carrier wherein the *composition is in a form suitable for intranasal delivery thereof* and wherein the peptide is present in an amount effective for treating a patient.
>
> The composition of the present invention *may exist in various forms*, for example, an oil-in-water emulsion, a water-in-oil emulsion, and a water-in-oil-in-water emulsion. The active compounds of the compositions of the present invention may exist in either the continuous or the dispersed phase or in both phases depending upon whether the compounds are hydrophilic, lipophilic, or amphiphilic.
>
> The composition of the present invention is delivered through a nasal spray applicator. If intra-nasal application is desired, the composition may be placed in an intra-nasal spray-dosing device or atomizer and may be applied by spraying it into the nostrils of a patient for delivery to the mucous membrane of the nostrils. A sufficient amount is applied to achieve the desired systemic or localized drug levels.
>
> For an intra-nasal spray, up to about 200 microliters is typically applied, with an application of about 50 to about 150 microliters being preferred, and 75 to 120 microliters most preferred. One or more nostrils may be dosed and application may occur as often as desired or as often as is necessary. In preferred embodiments, the nasal spray applicator is selected to provide droplets of the composition of a mean size of from about 10 microns to about 200 microns. More generally the droplet size is from about 30 microns to about 100 microns.

As another example, see 6,197,328 (Dott Research Labs). It states that the object of the invention is to provide a composition that can nasally administer physiologically active compound with higher bioavailability. It discloses that multiple proteins and peptides can be administered using its technology. It states:

> The amount of the above-mentioned physiologically active compounds to be contained in the composition of the present invention is not specifically limited and may vary with the individual active ingredient to be chosen, the disease to be treated, desired number of administration, desired effect of therapy, and so on. *Thus, when administering the composition of the present invention via the nasal route, the amount of the physiologically active compound to be administered can be determined on the basis of a comparison with other known preparation containing the same, in terms of bioavailability*. Therefore, when preparing the composition of the present invention, it is appropriate to have the physiologically active compound contained at a rate from 0.0001% to 30%, preferably from 0.01% to 20%, more preferably from 0.1% to 5.0%, per the 100% total weight of the composition.

As another example, US 6,440,392 (Unigene Laboratories) discloses an intranasal calcitonin formulation. Calcitonin, like desmopressin, is a peptide hormone. This patent states:

> . . . bioavailability for calcitonins, in particular salmon calcitonin, as determined in terms of blood-plasma concentration following nasal administration in accordance with the teachings of the present invention has been found to be surprisingly high.

As still another example, US 4,988,512 (Sandoz) discloses a nasal plug for peptide administration. This patent states:

> *The amount of agent carried* in the inserts of the invention will of course depend on the particular agent chosen . . . , the conditions to be treated, the desired frequency of administration, *the particular therapeutic effect required*, etc. The amounts required can be determined using conventional bioavailability comparisons of the nasal inserts of the invention and other e.g. known therapeutically effective forms containing the active agent.

and

> While the present invention is herein described primarily with reference to the administration of calcitonins, it is to be appreciated from what has been said above, that the invention is equally applicable to other pharmaceutically applicable peptide substances or other systemically active pharmacologically active agents. In its broadest

> aspect the invention is accordingly not to be understood as being in any way limited in relation to the pharmaceutically applicable peptide concerned.

These references are only four of many that a person of skill can consult for alternatives in producing a nasally administered form.

Applicant has also noted and the Examiner is well aware that there is a nasal desmopressin dosage form already on the market (see cited but not applied Minirin Nasal Spray document). On December 12, 2007, the FDA warned physicians and patients concerning such dosage forms:

> Certain patients taking desmopressin are at risk for developing severe hyponatremia that can result in seizures and death. Children treated with desmopressin *intranasal* formulations for primary nocturnal enuresis (PNE) are particularly susceptible to severe hyponatremia and seizures. As such, desmopressin *intranasal* formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatremic patients or patients with a history of hyponatremia. * * * *All* desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatremia.

(See http://www.fda.gov/cder/drug/InfoSheets/HCP/desmopressinHCP.htm)

The danger in conventional formulations highlighted by this FDA alert is precisely the problem applicant's dose forms address. Applicant submits that a serviceable embodiment of his invention could be produced simply by reducing the amount of active in this conventional nasal dosage form thereby reducing the amount of desmopressin delivered to the patient's blood stream so that a blood concentration maximized at around the upper end of the low dose range claimed. Without the exercise of invention, and with the application of only routine skill, one skilled in the art armed with the insights of the present invention could optimize such a formulation so as to reliably achieve a maximal blood concentration in the particular target population of, for example, 7 plus or minus 2 pg/ml, which might induce diuresis, for example, for six hours.

With respect to transdermal and intradermal dose forms, the art is equally developed, see, by way of non-limiting example, U.S. Patent 6,503,231 (Georgia Tech - see particularly section

titled "Drug Delivery"); U.S. 7,211,062 (TheraJect), and U.S. 7,302,293 and U.S. 2006/0093658 (both to Alza). U.S. 5,848,991 (Elan) discloses an intradermal drug delivery device. Note the summary of the invention which states: "such an intradermal drug delivery device permits the delivery of a variety of drugs including drugs of relatively large molecular size, and at slow rates which can be precisely controlled." Note also this patent mentions desmopressin specifically as one drug that can be delivered using the delivery device.

In the office action the Examiner asserts that "the examples presented are all outside the claimed dosage range." What the Examiner apparently meant to state was that the experimental work set forth in the examples was done using IV dosing while the claims exclude IV dose forms. In this respect, Applicant refers the Examiner to Example 8, tables 1-6 and Figures 1-9. These data specifically disclose administration to achieve a desmopressin blood concentration within the range claimed and show specifically the antidiuretic effect both in terms of increased urine osmolarity and decreased urine volume. The reason why this work was done using IV administration is that this dosing route is the best and most direct way for Applicant to test and support his low dose hypothesis in human volunteers. Such dosing results in the ability to know with certainty the amount of desmopressin that actually entered the bloodstream of the volunteers and enabled ready calculation of blood concentrations, which recently have been validated empirically. These experiments thus tested administration of known amounts of desmopressin, free of the complexities of bioavailability. Applicant submits these examples are not "outside the claimed dosage range."

The Examiner also suggests in his office action that "if such pharmacokinetic effects are unexpected, one would understand that this is an unpredictable effect. . . ." Applicant respectfully submits that he has provided the key to the unexpected effect – the maintenance of low blood concentration within the ranges claimed. The person of skill in the art, once this key is revealed, can without undue experimentation make numerous species of dosage forms to achieve the blood concentration, and know that the effect will be achieved.

Applicant submits that a person of skill in the art, upon reading applicant's specification, is enabled to make and use numerous embodiments of his claimed inventions without undue

experimentation, and accordingly that the 35 USC 112 rejection for alleged lack of enablement should be reconsidered and withdrawn.

Claims 1, 3, 4, 6, 7, 9, 27 and 28 stand rejected for indefiniteness

The Examiner holds that these claims violate the claim definiteness requirement of 112 second paragraph as they omit allegedly essential elements - the elements that are "specifically required to achieve the desmopressin plasma/serum concentration claimed."

In view of Applicant's explanation in the foregoing section on enablement, it should be apparent that applicant *does not regard the set of specific elements that may be used to achieve the plasma profile as an aspect of his claimed invention.* The inventions claimed herein do not involve some specific method or structure for achieving the claimed desmopressin blood concentration profiles. This is the domain of the skilled mechanic. Applicant's claimed invention does not involve the specific mechanism or structure through which the dose form achieves the blood concentrations, save that they must meet the limitations as recited in the various presented claims. The invention lies in the set of dosage forms that achieve, and maintain for a reasonable, and reasonably predictable time, by any known means or means yet to be invented, serum/plasma concentrations within the claimed range. If one manufactures and uses such forms, a novel, unobvious, unanticipated, and valuable effect is achieved – antidiuresis without substantial risk of hyponatremia.

Accordingly, no step essential to define applicant's invention is omitted. The specific structures and chemistries exploited to achieve the blood levels recited are no more a part of the invention than the specific way the desmopressin in the dosage forms is manufactured.

Applicant submits the claims particularly point out and distinctly claim the subject matter he regards as his invention. A persons of skill in the art upon reading the claims clearly is able to determine the metes and bounds of the subject matter claimed. The artisan knows how to make dosage forms to achieve a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per mL plasma/serum to about 10.0 picograms desmopressin per mL plasma/serum. He knows various techniques for measuring concentration of drugs in blood, and is familiar with technology addressing bioavailability issues. Accordingly, Applicant

submits there is no ambiguity in the presented claim language, and that under these circumstances this rejection should be reconsidered and withdrawn.

Claims 1, 6, 7, 9, 27 and 28 stand rejected as anticipated by Stanley (4,863,737)

U.S. Patent No. 4,863,737 to Stanley et al. discloses a candy matrix for transmucosal delivery through the mucous membranes of the mouth, pharynx, and esophagus of drugs, including a long list of actives, and desmopressin, which can be present in amounts ranging from 10 to 50 micrograms. The Examiner notes that Example 20 discloses a lollipop containing 20 micrograms of desmopressin for treatment of polyuria.

The claims as amended all have been limited to transdermal, intradermal or intranasal dose forms, and this alone is submitted to obviate the 102 rejection based on the Stanley reference, as it discloses no such forms. Applicant reserves the right to reintroduce in a continuation claims broad enough to embrace various transmucosal dosage form, including mucosal tissue of the mouth.

Furthermore, to the extent Stanley is continued to be applied to the claims as amended such a rejection is respectfully traversed for at least the following reason. During use of a lollipop dosage form, saliva production and swallowing will vary greatly among patients, varying amounts of the active will be transported to the gut (essentially never reaching the blood stream), and some unknown amount will be transported transmucosally into the circulation as Stanley et al suggest. As such, this reference does not literally or inherently disclose *establishment of a steady plasma/serum desmopressin concentration in the range* of from about 0.1 picograms desmopressin per ml plasma/serum to about 10.0 picograms desmopressin per ml. It contains no data or facts upon which one could know what level of desmopressin, if any, would or could be achieved by such dosage form in any individual.

The Examiner is referred to the previously submitted Nardi declaration, paragraph 15. Lollipop dose forms as disclosed in example 20 of Stanley would produce widely varying desmopressin blood concentrations, ranging from essential zero to a maximum well above the range claimed herein. As Dr. Nardi reported in his declaration:

> "Oral transmucosal bioavailability of desmopressin is in the range of 0.25%. This range is low and very broad as the oral mucosal (buccal) surface area and permeability vary among individuals, and because the dwell time of any dosage form in position adjacent

> the membranes in the mouth varies widely, with unknown amounts of the active in conventional buccal dosage forms being diluted in saliva and swallowed, and essentially lost by digestion in the stomach."

Accordingly, the dose form disclosed by Stanley does not inherently achieve and maintain desmopressin blood concentrations within the claimed range as required by the claims, and Stanley does not anticipate.

The Examiner states that "Products of identical chemical composition can not have mutually exclusive properties" and "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." Applicant agrees with these points, but submits they do not apply here, because the dose forms Applicant is claiming must be adapted to deliver and maintain a blood concentration within the claimed range. Both Stanley and Applicant's specification disclose oral transmucosal dosage forms of desmopressin, and the amount of active present in the respective forms overlap. However, Applicant's claims are limited to an unobvious and novel subgroup of the forms which deliver enough desmopressin and at a rate sufficient to establish the recited blood concentrations. The Stanley patent, including example 20, discloses no attempt to do this, does not recognize any advantage in doing so, and does not do so inherently. At best, the Example 20 dose form might produce such a blood concentration from time to time haphazardly in some people. Stanley accordingly does not anticipate Applicant's claims.

Claims 1, 3, 4, 9, 27 and 28 stand rejected as anticipated by Dixon

The Examiner asserts that "nothing physically distinguishes such injectable compositions [disclosed in Dixon] from those administered via intradermal . . . injection" and he reminds Applicant that "the claims are drafted as compositions and nothing precludes one from using it for a different intended use." He then asserts that "because the structural limitations [of the claims] are met" [by the disclosure of the reference] the properties which inure to dosage forms claimed by Applicant "would inherently occur." Applicant has read this passage of the office action carefully in an attempted to understand the Examiner's position, but despite his best efforts cannot see how the Examiner can hold that Dixon discloses every element of rejected

claims 1, 3, 4, 9, 27 and 28. Accordingly, to the extent this rejection is applied to the claims as amended, Applicant must respectfully traverse for the reasons which follow.

First of all, Applicant submits that it is incorrect that the structural limitations [of the claims] are met" [by the Dixon disclosure]. Every claim presented in this application specifically requires that the dosage forms be "adapted for" intranasal, transdermal, or intradermal administration. This is a *structural limitation* well understood by the skilled artisan, and means that the dosage form must be formulated and carried appropriately for administration by one of these dosage routes. Thus an intranasal dose might be delivered via a nasal injector or plug, which meters a proper amount of drug formulation comprising desmopressin and a carrier which may facilitate passage across nasal mucosal membranes. The injector would deliver an amount of the composition sufficient to result in a concentration of desmopressin within the claimed range in the bloodstream. Similarly, intradermal and transdermal dosage forms would comprise some form of skin patch or other device designed to be applied to, contact, or penetrate the skin, and to actively or passively deliver desmopressin through at least part of the skin tissue, again at rates and concentrations designed to deliver enough desmopressin to the bloodstream to achieve and maintain for some specified and desired time a concentration of desmopressin within the claimed range.

Because no dosage form is disclosed in Dixon that possibly would have the necessary properties or associated structure to enable intradermal, transdermal, or intranasal delivery, Applicant can only assume that the Examiner's view is that if the compositions used by Dixon were inhaled nasally by a patient, or placed on his skin, those compositions would inherently achieve the blood concentration required of the claimed dosage forms. Otherwise, the Examiner's assertion that the Dixon solution designed for IV administration is "adapted for" intranasal, transdermal, or intradermal use is clearly incorrect. But such a position ignores the fundamental nature of anticipation law. It also ignores that the Dixon paper:

- fails to disclose the nature of the formulation used in its study, and
- fails to address the established fact of bioavailability differences inherent in different routes of administration.

First, note that the fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Second, regarding the specific disclosure of Dixon, Applicant is unable to locate a description of how the desmopressin was formulated, and the Examiner has referenced no such disclosure. The disclosure Applicant could find potentially relevant to this point is that the volunteers were given "either saline or DDAVP (Ferring) intravenously . . . prepared by serial dilution" (see column 2 page 484). The *identity of the carrier* of the desmopressin IV doses is *not disclosed* (although it logically may be physiological saline). Furthermore, the *amount of carrier used is not stated* in the Dixon paper. Was the desmopressin administered as 1 ml of solution, 10 ml, or 100 ml? Was it a bolus injection or an infusion made over some period of time? Depending on the answers to these unanswered questions, the dosage forms administered could have had a volume of 0.1 ml, or 100 ml, or some other volume. In any event, it would be sheer happenstance were such doses to be suitable for intranasal, transdermal or intradermal administration. They would have to have been formulated in the correct volume, concentration, and with proper bioavailability characteristics so as to achieve the blood concentration range recited in the claims. But no such volume, concentration, or intranasal, transdermal, or intradermal bioavailability data is disclosed in Dixon. Furthermore, it is well known that aqueous solutions cannot effectively penetrate the skin. Accordingly, this rejection should be reconsidered and withdrawn.

If the Examiner believes that a telephone conversation with Applicant's attorney would expedite allowance of this application, the Examiner is cordially invited to call the undersigned attorney.

Respectfully submitted,

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